

Palliation of Allograft Vasculopathy With Transluminal Angioplasty

A Decade of Experience

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OBJECTIVES	The goal of this study was to examine the outcomes of percutaneous coronary interventions (PCI) and the predictors for restenosis after cardiac transplantation.
BACKGROUND	The role of PCI as definitive therapy for allograft coronary disease (ACD) remains contentious.
METHODS	Between January 1, 1990 and December 31, 2000, 62 patients (1.5 to 15.5 years after transplant) underwent 151 procedures resulting in PCIs of 219 lesions. Follow-up after PCI angiography was usually obtained at three and six months, then yearly. Repeat PCI was routinely done to lesions with >60% restenosis.
RESULTS	The primary procedural success was 97%. Repeat PCI occurred in 74 of 219 lesions (34%); PCI-related mortality was 2.6% (4 of 151). The freedom from re-PCI (of same vessel site) was 75% at six months, 65% at one year, and 57% at four years. The freedom from restenosis was 95% at one month, 81% at three months, and 57% at six months. Multivariate predictors of freedom from restenosis were the use of stents, higher anti-proliferative immunosuppressant dose, and an era effect. In the setting of one-vessel disease at first PCI, the two-year freedom from ACD death or graft loss was 74%, compared with 75% for two-vessel and 27% for three-vessel disease ($p = 0.009$).
CONCLUSIONS	Despite the increasing effectiveness of PCI for localized ACD, the survival after development of advanced ACD remains poor. Stents appear to increase effectiveness of PCI for ACD, but other factors in the current era contribute to improved outcomes. (J Am Coll Cardiol 2004; 43:1973–81) © 2004 by the American College of Cardiology Foundation

Allograft coronary disease (ACD) remains a predominant barrier to long-term survival after cardiac transplantation. There is a steady and linear risk of developing angiographically visible ACD from year one, so that by five years, over 50% of cardiac transplant recipients will have some disease (1). Beyond five years, the risk of developing angiographically visible severe disease increases proportionally, so that 29% of patients will have significant disease by nine years post-transplant (2). The risk of death from ACD also rises steadily after transplant and accounts for nearly 25% of all deaths between years 1 and 10 (1). Even discrete lesions >40% in the proximal or mid-major epicardial vessels, if left untreated, can lead to mortality rates exceeding 50% by three years (3). Once patients develop three-vessel or severe ACD, their risk of cardiac events (death or retransplantation) is substantial with the highest risk within one year of diagnosis (3).

Unfortunately, treatment of advanced disease is limited. Retransplantation is not an option for all, given the limited donor pool, and the results of bypass surgery for

this condition are generally poor (4). Percutaneous transluminal coronary angioplasty (PTCA) is an established modality for treatment of focal native coronary artery disease (CAD) and ACD, but its value in diffuse disease is not well established.

Numerous studies have examined the procedural efficacy of PTCA post-transplant, but most involve small (<30 patients) single-center experiences with few PTCA procedures (average 40 to 50) (4–6). From these studies, it appears that the initial procedural success is high (90% to 98%), and the incidence of restenosis is 30% to 100% for PTCA alone and 14% to 56% with stents (7–9). However, in many of these studies, the definitions for restenosis and the duration of follow-up differ, resulting in considerable variability in reported results. Short-term survival post-procedure is generally good with a one- to two-year mortality of 17% to 35% (4,6,9). Unfortunately, risk factors analyses for restenosis (one study) and longer-term survival data are generally lacking.

The purpose of the present analyses was to examine in a large series of post-transplant percutaneous coronary interventions (PCI) the outcomes of these procedures for localized disease, including primary procedural success, restenosis, and reintervention rates. We also sought to define the predictors for restenosis and gain insight into the potential value of PCI as part of an overall strategy to prolong graft survival after the development of ACD.

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Abbreviations and Acronyms

ACD	=	allograft coronary disease
AP	=	anti-proliferative
CAD	=	coronary artery disease
MLD	=	minimal luminal diameter
MMF	=	mycophenolate mofetil
PCI	=	percutaneous coronary intervention
PTCA	=	percutaneous transluminal coronary angioplasty

METHODS

Patients. All patients transplanted at the University of Alabama at Birmingham who had a PCI (PTCA alone, PTCA with stent) between January 1, 1990 and December 31, 2000 were included in this analysis. Thus, this study comprised 62 patients who underwent 151 procedures (trips to the angioplasty suite) resulting in PCI of 219 lesions. Angiographic follow-up was available in 174 (79%) of these procedures; 45 procedures had no angiographic follow-up because of death (10), retransplantation (7), primary procedural failure (6), or other (10).

Angiography. Measurements of lesions were made with electronic calipers, and minimal luminal diameters (MLDs) were determined. A calibration factor was determined as the ratio of the measured diameters of the diagnostic or guiding catheters to their known dimensions. The quantitative dimensions were then calculated as the product of the measured dimension by the calibration factor. The view with the worst stenosis was used for the initial lesion stenosis calculation. Whenever possible, the same angiographic views were used in follow-up films for restenosis calculations. The percent diameter stenosis was calculated as: (reference diameter – MLD)/(reference diameter) × 100. Procedural success was defined as a <50% residual stenosis and restenosis defined as >50% stenosis at the angioplasty site on follow-up angiography. Patients had annual coronary angiography according to current guidelines at the University of Alabama at Birmingham. Follow-up angiography to determine the need for reintervention was usually obtained at three and six months, then yearly. Repeat PCI was routinely applied to vessel sites with >60% restenosis.

Demographics and data collection. The demographic variables collected on all patients included age, race, gender, height, weight, body mass index, time since transplant, pretransplant heart disease, and time since initial diagnosis of ACD. Clinical variables collected included detailed history of immunosuppressants at time of procedure including type, dose, level (if appropriate), and duration of use before procedure; rejection history including total number and number of treated rejections since transplant and within six months of procedure; lipid levels closest to time of procedure; as well as the presence of diabetes mellitus, hypertension, history of tobacco use, and cytomegalovirus serology and infections. A detailed account of non-

Table 1. Demographic and Procedural Characteristics

Demographic characteristics	
Number of patients	62
Mean age at first PTCA, yr (±SD)	54 ± 13
Male gender, n (%)	47 (76)
Race, n (%)	
Caucasian	55 (76)
African American	7 (11)
Weight at first PTCA, kg (±SD)	88 ± 17
Clinical characteristics	
Cholesterol profile	
Total cholesterol, mg/dl (±SD)	223 ± 66
Triglycerides, mg/dl (±SD)	259 ± 184
Low-density lipoprotein, mg/dl (±SD)	126 ± 44
High-density lipoprotein, mg/dl (±SD)	44 ± 13
Immunosuppression*	
Mycophenolate mofetil, %	12
Azathioprine, %	69
Cytosine, %	12
Prednisone only, %	6
Other medications	
Beta-blockers, %	19
Angiotensin-converting enzyme inhibitors, %	38
Calcium-channel blockers, %	74
Aspirin, %	75
Procedural characteristics	
Total number of procedures	151
Total number of interventions	219
PCI 1990–1996, n (%)	85 (62)
PCI 1997–2000, n (%)	66 (44)
Stent, n (%)	84 (38)
No stent, n (%)	135 (62)
Periprocedural use of GP IIb/IIIa antagonists, n (%)	14 (9)
Periprocedural use of ticlid/plavix, n (%)	69 (46)

*Only four patients were not on calcineurin antagonist (cyclosporine or prograf).

GP = glycoprotein; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty.

immunosuppressant medications at time of procedure was also collected including use of angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, calcium channel blockers, and HMG-CoA reductase inhibitors. Procedural variables collected included percent stenosis, lesion location, stent use, and procedural medication use including thienopyridines (ticlid/plavix), aspirin, glycoprotein IIb/IIIa antagonists, and heparinoids.

Statistical analyses. Kaplan-Meier and three-phase parametric analysis in the hazard function domain (11) were used to examine the event restenosis (defined as recurrence of 50% or greater stenosis after a “successful” PCI [<50% stenosis on follow-up angiogram]) and death or graft loss due to ACD. Risk factors for restenosis were explored by multivariable hazard function analysis. The variables entered into the analysis are listed in the Appendix Risk factors were retained in the model if the p value was <0.05. Follow-up was restricted to eight months after PCI.

RESULTS

Demographics. Baseline demographic, clinical, and procedural variables are represented in Table 1. Mean time from transplant to first PCI was 7.2 years (range, 1.5 to 14.5

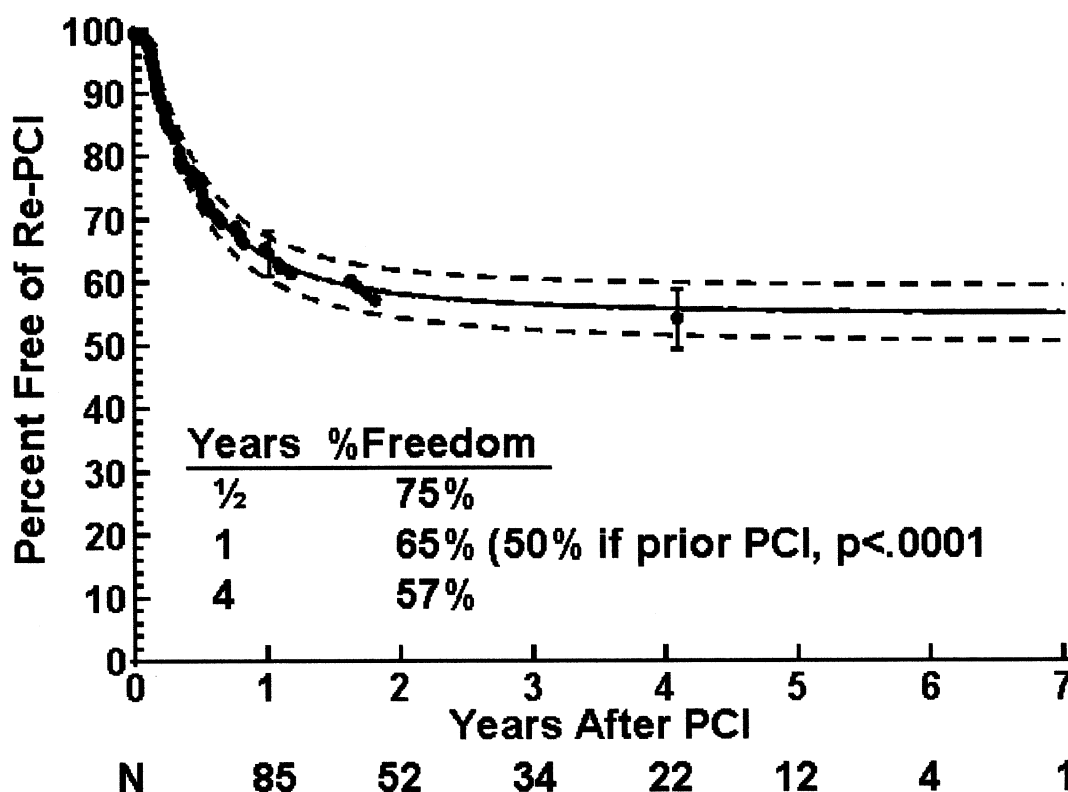


Figure 1. Kaplan-Meier depiction of the event re-percutaneous coronary intervention (PCI) for the 219 angioplasties. The parametric hazard model is plotted as the **smooth curve**. **Error bars** and parametric confidence limits are 70%. The number of vessels still at risk of re-PCI is noted at the bottom of the plot.

years). Mean time from first PCI to follow-up angiography was two months (range, 1.3 to 8 months) with 75% of procedures having follow-up angiograms between 5.5 to 8 months.

Procedural outcomes. Primary procedural success was 97% (213 of 219 lesions). Periprocedural mortality was low at 2% (4 of 151 procedures). There were no incidences of acute stent thrombosis. Primary re-PCI for restenosis occurred in 34% of initially treated lesions (74 of 219). **Figure 1** depicts the freedom from re-PCI over time. As noted, the majority of the repeat procedures were performed within the first year after the primary procedure. The freedom from re-PCI was 75% at six months, 65% at one year, and 57% at four years. There was a 95% freedom from restenosis at one month, 81% freedom at three months, and only a 57% freedom by six months (**Fig. 2**).

Risk factor analysis for restenosis. Multivariate risk factor analysis of potential risk factors (demographic, clinical, and procedural variables) for restenosis demonstrated only four significant factors (**Table 2**). The use of stents, higher dose “anti-proliferative” (AP) immunosuppressant drugs (azathioprine ≥ 1 mg/kg/day or mycophenolate mofetil [MMF] ≥ 3 g/day), and having PCI after 1997 were negative predictors of restenosis. Positive risk factors for developing restenosis included having a PCI before 1997 and a more severe initial stenosis at time of PCI.

The impact of stents was apparent within the first few

months after a PCI (**Fig. 3**). The freedom from restenosis at three and eight months was 93% and 61% with stent use and 67% and 28% without stent use, respectively. A similar degree of improvement was noted with the use of a higher-dose AP immunosuppressant agent (**Fig. 4**). In the group using higher dose APs, there was a 88% and 60% freedom from restenosis at three and eight months compared with 70% and 30% in the lower or no AP dose group. An “era effect” on the risk of restenosis was apparent after 1997 (**Fig. 5**). In the post-1997 group, there was a 97% and 60% freedom from restenosis at three and eight months compared with 64% and 30% before 1997.

The interactions between risk factors are depicted in **Figure 6**. The predicted freedom from restenosis for a patient undergoing a PCI after 1997 without a stent and on a lower dose or no AP immunosuppressant was 80% and 26% at three and eight months, respectively. When a higher-dose AP was utilized, the freedom from restenosis increases to 94% and 71% at three and eight months, respectively. If a stent is added, a similar effect is noted with a 93% and 67% freedom from restenosis at three and eight months, respectively. The most striking effect was noted when both a stent and a higher-dose AP were used in the modern era of PCI. The freedom from restenosis with this combination was 98% at three months and 90% at eight months.

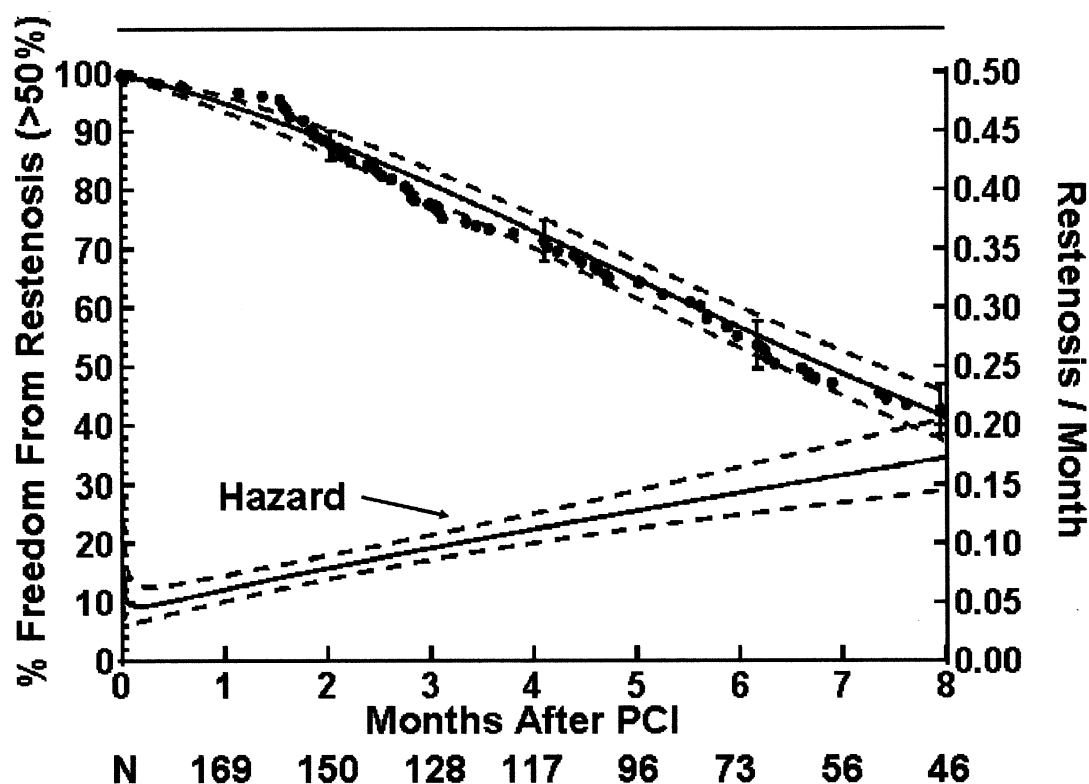


Figure 2. Kaplan-Meier depiction of the event restenosis for the 219 angioplasties (only 174 had follow-up angiograms). The parametric hazard model is plotted (survival and hazard) as the **smooth curve**. **Error bars** and parametric confidence limits are 70%. The number of vessels still at risk of restenosis is noted at the **bottom of the plot**. PCI = percutaneous coronary intervention.

Era differences. In an attempt to understand this prominent era effect, multiple patient-related procedural and clinical variables were compared in patients undergoing a PCI before and after 1997 (Table 3). There were no significant patient-related differences. However, there were many notable differences in procedural and clinical variables between these two eras. Subsequent to 1997, there was a smaller degree of residual stenosis after procedure (22% vs. 8%, $p < 0.001$), a higher pre-, post-MLD difference (50% vs. 65%, $p < 0.001$), as well as a significantly greater use of thienopyridines and glycoprotein IIb/IIIa antagonist use. In addition, there were several significant clinical changes between these two eras. In the post-1997 era, there was a greater use of Neoral brand of cyclosporine and HMG-CoA reductase inhibitors and less use of Cytoxan and calcium channel blockers. In addition, cyclosporine levels and triglyceride levels were significantly lower in the post-1997

era. It should be noted, however, that none of these variables were individually identified as risk factors for restenosis (Table 2).

Event-free survival analyses. Twenty-five deaths occurred in this series of patients, of which eight (32%) were related to ACD. In addition, there were 10 re-transplants all due to advanced CAD. The freedom from death or retransplantation was 71% at one year and 34% at five years after intervention. This event rate was then stratified by number of diseased vessels. The freedom from death or graft loss was 27%, 75%, and 74% at two years in patients with three-, two-, and one-vessel disease, respectively. At five years, the freedom from death or graft loss was 0%, 42%, and 64% in patients with three-, two-, and one-vessel disease, respectively.

DISCUSSION

This analysis represents the largest reported experience of PCIs in cardiac transplant recipients to date. This study supports the contention that PTCA with stents is effective in relieving focal stenoses in patients with ACD. Initial procedural success is high with low periprocedural mortality. The risk of both restenosis and repeat PTCA is highest in the first six months after therapy. The use of stents, higher dose AP immunosuppressants, and modern procedural techniques have markedly improved the initial result

Table 2. Multivariate Predictors of Restenosis for PCI of Allograft Coronary Disease

Risk Factors for Restenosis	Relative Risk	p Value
Use of stent	-3.3	<0.0001
High dose antiproliferative*	-1.9	<0.0001
PCI before 1997	2.6	0.0002
% Stenosis pre-PCI†	2.3	0.0012

*Azathioprine ≥ 1 mg/kg/day or mycophenolate ≥ 3 g/day; †relative risk for 90% vs. 60% pre-PCI stenosis.

PCI = percutaneous coronary intervention.

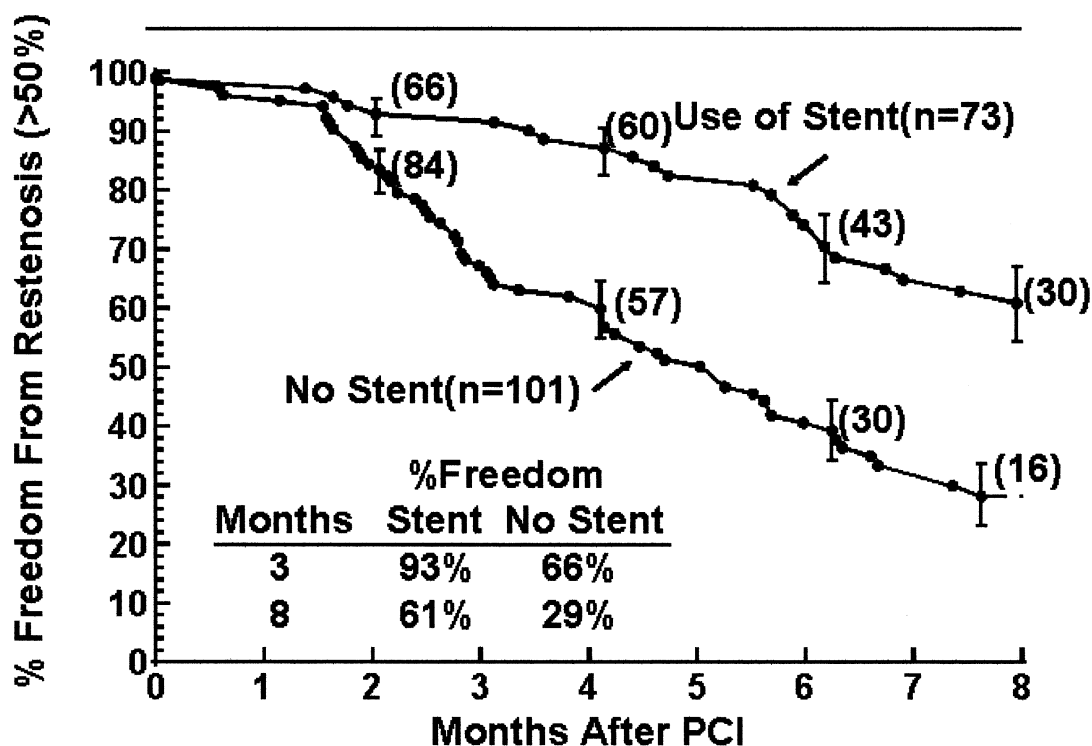


Figure 3. Kaplan-Meier depiction of the event restenosis for the 219 angioplasties (only 174 had follow-up angiograms) stratified by use of a stent. Error bars are 70%. The number still at risk at selected time points is indicated in parentheses. PCI = percutaneous coronary intervention.

and reduced the incidence of restenosis. The combination of stents and higher-dose immunosuppressants in the post-1997 era led to a clinically important freedom from re-

stenosis of 90% by six months. In several smaller studies of cardiac transplant recipients undergoing PCIs, a cumulative of 83 patients underwent PTCA without stenting and

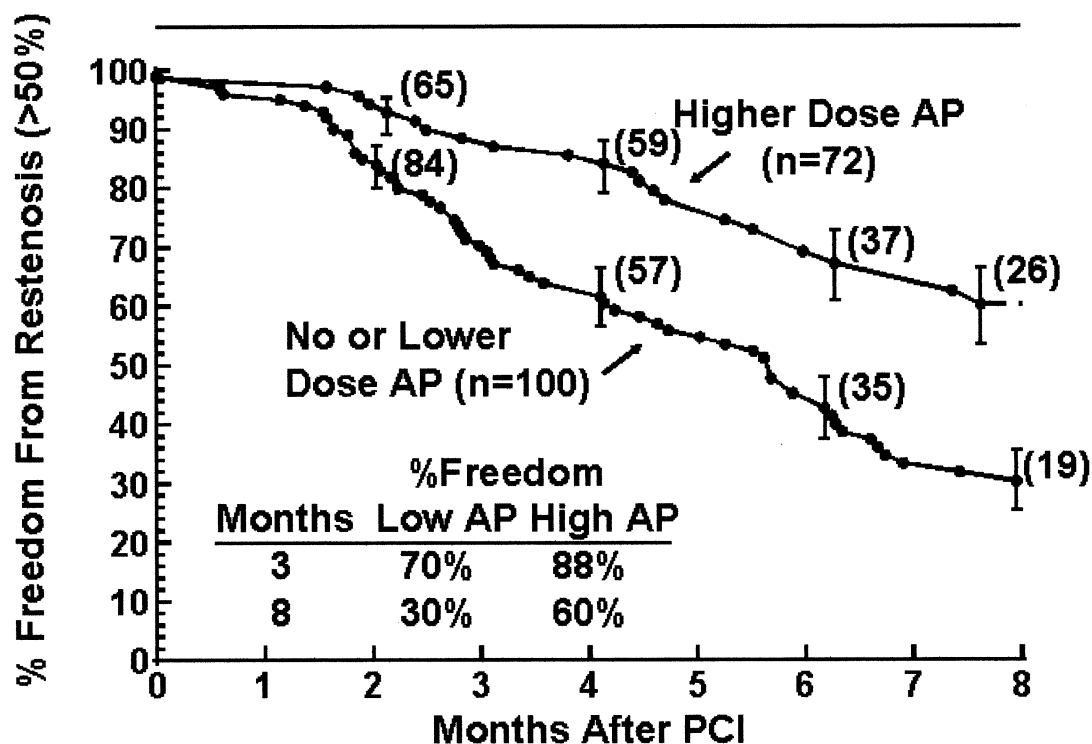


Figure 4. Kaplan-Meier depiction of the event restenosis for the 219 angioplasties (only 174 had follow-up angiograms) stratified by use of high-dose anti-proliferatives (AP). Error bars are 70%. The number still at risk at selected time points is indicated in parentheses. PCI = percutaneous coronary intervention.

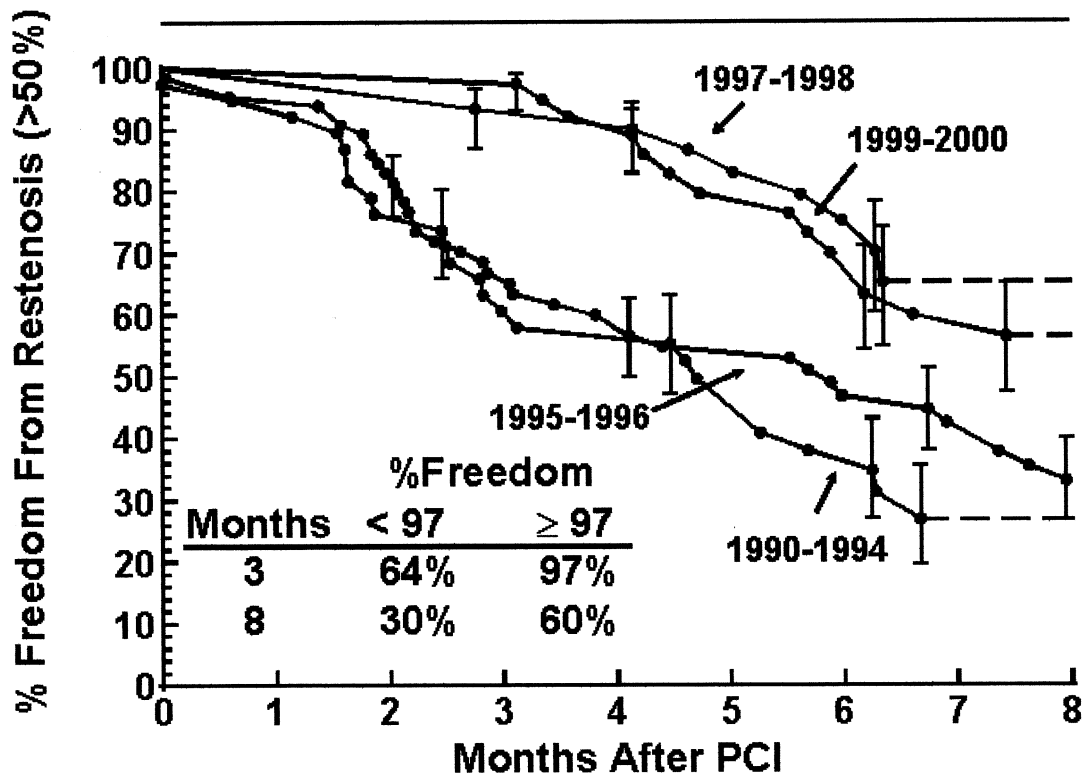


Figure 5. Kaplan-Meier depiction of the event restenosis for the 219 angioplasties (only 174 had follow-up angiograms) stratified by the era in which the percutaneous coronary intervention (PCI) was done. **Error bars** are 70%. The number still at risk at selected time points is indicated in **parentheses**.

demonstrated restenosis rates of 14% to 61% at four to seven months (7-9,12-14). In addition, one multicenter study of 35 patients undergoing PTCA of 95 lesions demonstrated a 55% restenosis rate at seven months. In several later studies in patients undergoing PTCA alone, the restenosis rate at two to six months ranged from 67% to 100% (10,15,16). Unfortunately, in many of these studies, the definitions for restenosis and the duration of follow-up differed, resulting in considerable variability in the restenosis rate. However, it is clear that the restenosis rates are generally higher than reported for native-vessel CAD.

The use of stents has greatly impacted the success of PTCA in the treatment of native-vessel CAD with reduction of procedural complications and improvement in late clinical outcomes (17). The beneficial effects of stenting compared with PTCA at six months are related to a reduction in restenosis rate by 30% and the need for surgical revascularization by 50% (18). Restenosis after PTCA results from arterial remodeling and late vessel contraction that accounts for >60% of late lumen loss (19), both of which may be favorably affected by stenting.

Our analysis is in concert with available studies in heart transplant recipients examining the benefit of PTCA with stenting in which restenosis rates at 6 to 12 months are consistently lower with the addition of stents (10,15,16). We found a significant reduction in the freedom from restenosis both early and late after PTCA with nearly a 50% reduction in restenosis at eight months. In addition, similar

to the small series on stenting for ACD reported by Heublein and Jain (5,6), there were no incidences of acute stent thrombosis. In light of this, we recommend routine use of stents during PTCA for transplant patients with significant focal ACD and appropriate anatomy for such a procedure.

One of the most interesting findings of this study was the improved procedural outcome for PCIs performed after 1997, a finding also noted in the literature on native-vessel PCI. Registries of PCIs for native-vessel CAD clearly demonstrate a stepwise improvement in the in-hospital clinical success rates from 82% in the mid-1980s, to 88% in the early 1990s, to 92% in the late 1990s (20-22). The restenosis rate also decreased from 38% in the early 1990s to 13% in the late 1990s. This trend is also noted for PCIs of focal ACD with improved restenosis rates of up to 25% in the late 1990s (5).

There have been many procedural and nonprocedural changes in PCI and post-PCI care over the past 10 years, which may cumulatively explain this notable improvement in procedural outcome. The multivariable model did not identify specific era-related variables (other than the era itself) that were predictive of improved restenosis rates, but several factors may have contributed. It appears that the specific reduction in restenosis paralleled the achievement of larger post-PCI lesion MLD, especially if the residual stenosis was <20% (23-25). An increase of mean postprocedural MLD from 1.67 mm in the early 1990s to 2.89 mm

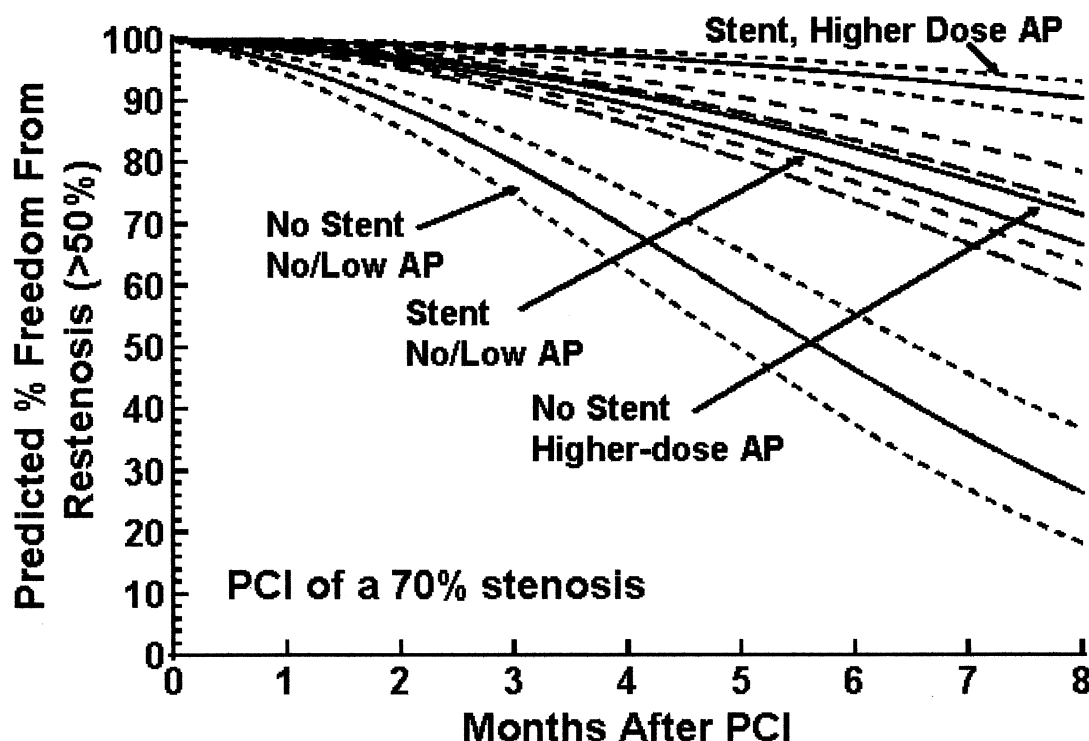


Figure 6. Parametric prediction from the three-phase hazard model with 70% confidence limits. The pre-percutaneous coronary intervention (PCI) stenosis is set at 70%, and the era is set at 1997 or later. The curves represent the predicted probability of restenosis for all combinations of the remaining risk factors use of stent (yes/no) and high-dose anti-proliferatives (AP) (yes/no).

in the late 1990s is clearly documented in the native CAD literature. Such was also the case in our series of PCIs in cardiac transplant recipients with the achievement of larger MLDs in the modern era. It appears that this more favorable procedural success seems to parallel the more frequent use of coronary stents, but may also be due to other factors like higher inflation pressures during the intervention (26–28).

In addition to these procedural advances, the introduction and widespread use of periprocedural glycoprotein IIb/IIIa (29) and thienopyridines (30) might also contribute to this era effect. The greater use HMG-CoA reductase inhibitors and lower triglyceride levels in our study in the post-1997 era could be important because higher triglyceride levels are associated with ACD (31) and with adverse vascular remodeling. HMG-CoA reductase inhibitors are vasoprotective, both in their ability to favorably affect lipids and inhibit smooth muscle cell activity (32). In addition, they appear to

be immunomodulatory, which could also theoretically lead to a reduction in restenosis rates, by altering endothelial activity and smooth muscles cell hyperactivity (33,34). Clinically, the HMG-CoA reductase inhibitor pravastatin, started within two weeks of transplantation, is associated with a lower incidence of ACD at angiography and autopsy (35).

The most interesting and novel immunosuppressant finding from this study, however, is the reduction in restenosis noted with higher doses of AP agents such as azathioprine and MMF. Although a preliminary and post-hoc finding, the effect of these agents on restenosis is intriguing. In addition to its and T-cell and B-cell effects, MMF also can inhibit growth factor-induced smooth muscle proliferation (36), which is a critical component of restenosis, particularly after stenting (37). In a study of heart transplant recipients, those patients receiving MMF had a significantly lower rate on intimal proliferation compared with azathioprine (38). In addition, in a rabbit model of atherosclerosis, the administration of MMF significantly reduced neointimal smooth muscle cell accumulation and plaque development (39). Thus, one of the mechanisms by which MMF may ameliorate the development of restenosis after stenting is through its actions on smooth muscle cell movement and proliferation. The specific mechanism for the presumed protective effect of azathioprine is less apparent.

Study limitations. As noted in prior studies on this topic, the influences generated by this study must be viewed with

Table 3. The Era Effect on PCI of Allograft Coronary Disease

Procedural Variables	Clinical Variables
Post-PCI stenosis less	Neoral/celcept use increased
Pre/post differences greater	Cytoxan use decreased
Stent use increased	Cyclosporine A levels lower
	Triglyceride levels lower
	Statin use increased
	Calcium channel blocker use decreased
	Ticlid/plavix/GP IIb/IIIa use increased

GP = glycoprotein; PCI = percutaneous coronary intervention.

the realization that it is retrospective in nature, uncontrolled, and the result of a single institution's experience. This study is also confounded by the inherent complexity of CAD in the transplanted heart. Although the focus of this study was PCIs as a therapy for ACD, only patients who actually underwent PCI were included in the analysis. The large "denominator" of patients with ACD includes many patients not treated by PCI, who were not part of this analysis. Patients undergoing PCI for ACD form a heterogeneous group among transplant institutions, in that considerable differences exist for selection of patients and angiographic lesions for this procedure. Thus, inferences from this study may not be generally applicable to the whole heart transplant community.

Allograft coronary disease is a life-long threat to heart transplant recipients and will require multiple avenues of therapy to suppress or treat the multitude of contributing factors. Percutaneous transluminal coronary angioplasty with stenting will only be of lasting therapeutic value if the promising outcomes of the most favorable groups are sustained over years. The eight-month follow-up is too short to gain meaningful insights into two- and three-year outcomes. The impact of higher-dose azathioprine or MMF therapy (perhaps reflecting the value of AP agents) is intriguing, but it must be remembered that this dosing data was collected at the time of PTCA intervention and does not necessarily reflect the overall or average AP dose since transplant or before the development of ACD.

However, the present study provides an element of rational hope that such interventions could have an important impact on certain aspects of this crippling post-transplant malady.

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APPENDIX

For the Table of variables for multivariable analyses of time to restenosis after successful PCI, please see the June 2, 2004, issue of *JACC* at www.cardiosource.com/jacc.html.